

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/026431

International filing date (day/month/year)
06.08.2004

Priority date (day/month/year)
06.08.2003

International Patent Classification (IPC) or both national classification and IPC
A61K39/02, A61K39/385, A61K39/39

Applicant
THE GOVERNMENT OF THE UNITED STATES OF AMERICA ...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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10/566898

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/026431

IAP20 Rec'd PCT/TO 01 FEB 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-14
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-14
Industrial applicability (IA)	Yes: Claims	1-14
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

International application No.

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Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: LEE C-J: "Quality control of polyvalent pneumococcal polysaccharide-protein conjugate vaccine by nephelometry" BIOLOGICALS, ACADEMIC PRESS LTD., LONDON, GB, vol. 30, no. 2, June 2002 (2002-06), pages 97-103
- D2: US-A-4 356 170 (JENNINGS ET AL) 26 October 1982 (1982-10-26)
- D3: BARTOLONI ANTONELLA ET AL: "Immunogenicity of meningococcal B polysaccharide conjugated to tetanus toxoid or CRM197 via adipic acid dihydrazide" VACCINE, vol. 13, no. 5, 1995, pages 463-470
- D4: SHAFER D E ET AL: "Activation of soluble polysaccharides with 1-cyano-4-dimethylaminopyridinium tetrafluoroborate (CDAP) for use in protein-polysaccharide conjugate vaccines and immunological reagents. II. Selective crosslinking of proteins to CDAP-activated polysaccharides" VACCINE, BUTTERWORTH SCIENTIFIC, GUILDFORD, GB, vol. 18, no. 13, January 2000 (2000-01), pages 1273-1281
- D5: MULARD L ET AL: "Vaccins polysaccharidiques" ANNALES DE L'INSTITUT PASTEUR ACTUALITES, vol. 12, no. 2, May 2002 (2002-05), pages 37-54

Novelty and inventive step for invention 1 (Articles 33.1, 33.2 and 33.2 PCT)

The subject matter of claims 1-14 is directed to methods for preparing conjugate vaccines by reacting an aldehyde activated polysaccharide (CHO-PS) with a hydrazine activated protein.

Document D1 discloses similar method. Nevertheless, the following differences can be found between the methods described in the prior art and the method disclosed in the

present application:

D1 does not disclose the following steps:

- (a) pH specification of 5-7 for the conjugation reaction,
- (b) neutralizing unreacted aldehyde groups

The subject matter of claims 1-14 is therefore new over the cited prior art.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and discloses method to prepare conjugate vaccines from which the subject-matter of claim 1 differs in the aforementioned features (a) and (b).

The problem to be solved by the present invention may therefore be regarded as providing a better conjugation method.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

The aforementioned features (a) and (b) would be regarded by the skilled person as a normal option to include in the method disclosed by D1.

In addition, the aforementioned features (a) and (b) cannot be linked to any surprising and advantageous effect.

The subject matter of claim 1 therefore lacks an inventive step.

The subject matter of dependent claims 2-14 does not contain any features which, in combination with the features of claim 1, meet the requirements of the PCT in respect of inventive step, the reasons being as follows:

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Each feature added in the dependant claims (such as specification of the oxidizing agent, the carrier protein, the purification of the conjugate vaccine) would be regarded as normal option to be included in a method for preparing a conjugate vaccine.

In addition, none of the feature introduced with the dependant claims can be linked to a surprising and advantageous effect.

Industrial applicability (Articles 33.1 and 33.4 PCT)

The subject matter of claims 1-14 relates to methods to prepare conjugate vaccines and is therefore susceptible of an industrial application.

Further remarks

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 to D5 is not mentioned in the description, nor are these documents identified therein.

The relative term "about" used in claim 1 has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of the claims unclear, Article 6 PCT.